2003-449257/42 B02 **TAKE 2001.09.25**
TAKEDA CHEM IND LTD *WO 2003035650-A1
2001.09.25 2001-290675(+2001JP-290675) *(2003.05.01)* C07D 491/048, A61K 31/4741, 31/497, 31/501, 31/506, 31/55, 31/554, A61P 3/04, 3/10, 9/04, 9/10, 11/00, 11/06, 13/12, 15/00, 17/02, 17/06, C07F 9/6561, C07D 519/00, A61P 19/02, 19/10, 25/00, 25/24, 25/28, 27/02, 29/00, 31/18, 37/02, 37/06, 37/08, 43/00

Use of new and known compounds having tricyclic partial structure as entry inhibitors for treating e.g. HIV infections (Jpn)

C2003-119260 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW) R(AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW)
Addnl. Data: KAWANO Y, FUJII N, KANZAKI N, IIZAWA Y
2002.09.24 2002WO-JP09760

B(6-E5, 14-A1, 14-A2B1, 14-E11, 14-F1A, 14-F2B, 14-F7, 14-G3, 14-J1A1, 14-J1A4, 14-N1, 14-N3, 14-N10, 14-N17B, 14-S4) .8

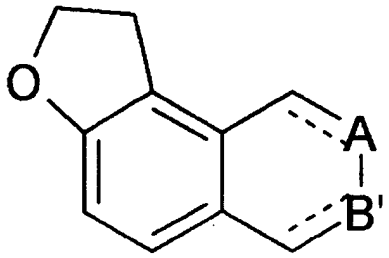
NOVELTY

Use of compounds having a tricyclic partial structure (I) is

claimed as entry inhibitors.

DETAILED DESCRIPTION

Use of compounds having a tricyclic partial structure of formula (I) or their salts is claimed as entry inhibitors.



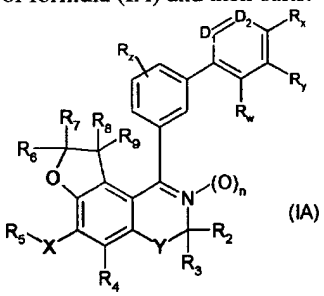
(I)

one of A and B' = C and the other = N.

An INDEPENDENT CLAIM is also included for tricyclic compounds

WO 2003035650-A+

of formula (IA) and their salts.



(IA)

D_1, D_2 = CH or N

R_2, R_3 = H, acyl or optionally substituted hydrocarbyl, or

$R_2 + R_3$ = 3-8 membered cyclic group;

R_4 = H, CN, acyl or optionally substituted hydrocarbyl or OH;

R_5 = H, halo or optionally substituted 1-3 C alkyl, 6-14C aryl or heterocyclyl;

R_6-R_9 = H or optionally substituted hydrocarbyl, or

$R_6 + R_7$ = 3-8 membered cyclic group;

X = a bond, O, S, SO, SO_2 or optionally substituted N;

Y = optionally substituted methylene;

R_w = H, 1-6C alkyl or optionally esterified carboxyl;

R_x = NH_2, $NHCOR_{x1}$, OH, 1-6C alkoxy (optionally substituted by COOH, 1-6C alkoxycarbonyl or mono-1-6C alkylcarbamoyl) or mono-1-6C alkylcarbamoyl;

R_{x1} = 1-6C n-alkyl or 7-16C aralkyl;

R_y = H or halo;

R_z = H, OH, NH_2, 1-6C alkoxy (optionally substituted by COOH or 1-6C alkoxycarbonyl), CN, COOH, 1-6C alkoxycarbonyl or carbamoyl, and

n = 0 or 1,

provided that:

(1) D_1 and D_2 are not both N; and

(2) the following compounds are excluded:

(a) 3'-(3,4,8,9-tetrahydro-6-methoxy-3,3,8,8-tetramethylfuro[2,3-h]isoquinolin-1-yl)[1,1-biphenyl]-4-amine;

(b) N-[3'-(3,4,8,9-tetrahydro-6-methoxy-3,3,8,8-tetramethylfuro[2,3-h]isoquinolin-1-yl)[1,1-biphenyl]-4-yl]acetamide;

(c) N-[3'-(3,4,8,9-tetrahydro-6-methoxy-3,3,8,8-tetramethylfuro[2,3-h]isoquinolin-1-yl)[1,1-biphenyl]-4-yl]propanamide;

(d) N-methyl-3'-(3,4,8,9-tetrahydro-6-methoxy-3,3,8,8-

WO 2003035650-A+/

tetramethylfuro[2,3-h]isoquinolin-1-yl)[1,1-biphenyl]-4-carboxamide;

(e) 3'-(3,4,8,9-tetrahydro-6-methoxy-4,4,8,8-tetramethylfuro[2,3-h]isoquinolin-1-yl)[1,1-biphenyl]-4-amine, and

(f) N-[3'-(3,4,8,9-tetrahydro-6-methoxy-4,4,8,8-tetramethylfuro[2,3-h]isoquinolin-1-yl)[1,1-biphenyl]-4-yl]acetamide.

ACTIVITY

Anti-HIV; Immunomodulator; Antidiabetic; Antiarteriosclerotic; Neuroprotective; Antibacterial; Antipsoriatic; Osteopathic; Antidepressive; Cerebroprotective; Nootropic; Anorectic; Cardiant; Antiallergic; Antianginal; Hypotensive; Nephropathic; Ophthalmological; Endocrine.

MECHANISM OF ACTION

Phosphodiesterase-Inhibitor-4.

In assays using HEK293 cells, N-methyl-3'-(3,4,8,9-tetrahydro-6-methoxy-3,3,8,8-tetramethylfuro[2,3-h]isoquinolin-1-yl)[1,1-biphenyl]-4-carboxylic acid (Ia) exhibited an IC_{50} value for entry of 7.5 nM.

USE

Used as entry inhibitors and phosphodiesterase-4 inhibitors for treating and preventing HIV infection and AIDS (claimed). (I) Are also useful for treating and preventing e.g. immunological diseases, diabetes, arteriosclerosis, multiple sclerosis, toxemia, psoriasis, osteoporosis, depression, diseases associated with cerebral vascular occlusion, Alzheimer's disease, obesity, heart failure, pulmonary fibrosis, allergic diseases, angina pectoris, myocardial infarction, hypertension, nephropathies, eye disease and male and female sexual dysfunction.

ADVANTAGE

(I) Have good activity and reduced toxicity.

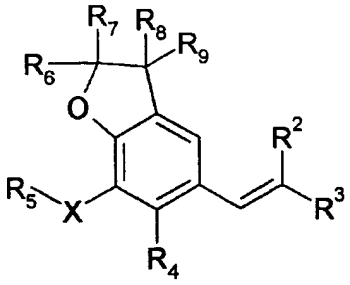
ADMINISTRATION

The dosage is 0.01-100 (preferably 0.05-10) mg/kg/day orally or by injection.

WO 2003035650-A+/

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Preparation of (IA) comprises e.g. reacting a tricyclic compound of formula (VIII) with R_1CN or R_1CONH_2 to give (IA; Y = CH_2 or CH(OH); n = 0).



(VIII)

(675pp2533DwgNo.0/0)

WO 2003035650-A/3